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Position paper

Consensus statement* on the treatment of allergic rhinitis

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1. Introduction

Allergic rhinitis (AR) is a high-prevalence disease in many developed countries, affecting about 10–20% of the general population (1–5). Several studies based on questionnaire and objective testing or medical examination indicate an increasing prevalence of AR in European countries over the last decades (6, 7).

AR is characterized by nasal itching, sneezing, watery rhinorrhoea, and nasal obstruction. Additional symptoms such as headache, impaired smell, and conjunctival symptoms can be associated. According to the time of exposure, AR can be subdivided into perennial, seasonal, and occupational disease. Perennial AR (PAR) is most frequently caused by dust mites and animal dander. Seasonal AR (SAR) is related to a wide variety of pollen allergens including grasses, *Parietaria*, *Ambrosia*, *Artemisia*, birch, olive, hazelnut, and cypress. The morbidity of SAR obviously depends on the geographic region, the pollen season of the plants, and the local climate.

Several other conditions can cause similar symptoms and are referred to as nonallergic (noninfectious) rhinitis: NARES (nonallergic rhinitis with eosinophilia syndrome); aspirin sensitivity; endocrine, occupational, postinfectious, and side-effects of systemic drugs; abuse of topical decongestants (rhinitis medicamentosa); and idiopathic rhinitis. Furthermore, diseases such as nasal polyposis, chronic sinusitis, cystic fibrosis, Wegener's disease, benign or malignant tumours, etc. have to be excluded carefully. Therefore, current guidelines (4) emphasize the importance of an accurate diagnosis of patients presenting with rhinitis symptoms. In fact, several causes may commonly coexist in the same

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patient, requiring separate consideration. The diagnosis of allergic rhinitis is frequently straightforward, but may also be very complex and difficult. The mainstay is an accurate history including an allergy history, based on familial and personal history, recent clinical aspects, and prior treatment. The possible presence of lower respiratory tract disease, skin symptoms, or pollen-related food allergies should always be investigated, since they are commonly associated with rhinitis. This is followed by a clinical examination of the nose. A major advance has been the introduction of rigid and flexible nasal endoscopes and, if sinusitis is considered, the availability of CT scanning.

When an allergic pathogenesis of the disease is suspected, the skin prick test (SPT) with standardized allergens should be performed. The measurement of allergen-specific IgE in serum (as single allergens or groups) is a useful diagnostic approach in selected cases (skin test with difficult interpretation or not feasible, children, allergen not available for SPT, etc.). As sensitization to an allergen does not necessarily mean that the individual patient suffers from clinical disease, the clinical relevance of skin or specific IgE results should be demonstrated before introducing therapies such as immunotherapy or environmental control. Whereas the clinical relevance in SAR usually can be demonstrated by carefully analysing patient history, nasal allergen challenge tests may be useful in PAR. Allergen-specific diagnosis (as well as therapy) should be based on purified standardized allergen extracts.

AR appears to impose variable restrictions on the physical, psychologic, and social aspects of patients' lives, and may have an impact on their careers. AR is underestimated as a cause of suffering and impaired quality of life (8–10). If symptoms of AR are not well controlled, they may contribute to learning problems and sleep disturbances (11, 12).

For AR, direct yearly costs are estimated at 1.0–1.5 billion Euro, while indirect costs are estimated at 1.5–2.0 billion Euro in Europe (13). Finally, the possible association between AR and other conditions including asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection, and even dental malocclusion should be considered in evaluating the socio-economic impact of the disease (14).

Table 1. Characteristics of allergic rhinitis

Characteristic	Seasonal	Perennial
Obstruction	Variable	Always, predominant
Secretion	Watery, common	Seromucous, postnasal drip, variable
Sneezing	Always	Variable
Smell disturbance	Variable	Common
Eye symptoms	Common	Rare
Asthma	Variable	Common
Chronic sinusitis	Occasional	Frequent

In recent years, new information on the pathophysiologic mechanisms underlying allergic inflammation has accumulated. Based on these recent data, the therapeutic strategies have been partly modified or improved, and new drugs or new routes of administration, dosages, and schedules have been studied and validated. Intended for the specialist as well as the general practitioner, this paper presents the state of the art of AR treatment, and provides a well-documented review of the drugs available and their place in the management of the disease.

2. Mechanisms of AR

AR results from IgE-mediated allergy, associated with cellular inflammation of the nasal mucosa of variable intensity. The mechanisms of AR have been largely clarified within the last 15 years from studies in naturally occurring disease and by the use of nasal challenge models in which cell infiltration and cell activation have been assessed (15–18). These studies highlight the presence of eosinophilic airway inflammation and identify the enhanced expression of endothelial and epithelial adhesion molecules (19, 20), as well as chemokines and cytokines (21, 22). The release of mediators from infiltrating leukocytes as well as resident tissue cells, such as mast cells, is implicated in both the symptoms and the development of nasal nonspecific hyperreactivity.

Histamine appears to be a major mediator released by mast cells in seasonal and perennial allergen exposure (23), but other mediators such as leukotrienes, prostaglandins, and kinins may also contribute to the symptomatology through their interaction with neural and vascular receptors (24, 25). In addition to these events, there is also neural involvement in the disease, with neuropeptide release from cholinergic and peptidergic nerves. Some different aspects of the two forms of AR are summarized in Table 1.

The enhanced expression of TH2-like cytokines, such as interleukin (IL)-4 and IL-5, within the nasal mucosa, generated by T cells, as well as mast cells, is a hallmark of AR and is relevant to the selective recruitment and survival of eosinophils (26, 27). The local generation of cytokines such as IL-5 and GM-CSF by eosinophils themselves, along with the generation of cytokines and chemokines by the epithelium, leads to the persistence of the eosinophil within the tissue. The epithelium is increasingly recognized as an active cell population, providing cytokines and chemokines relevant to the local tissue cell recruitment (28), with an accumulation of mast cells, basophils, eosinophils, and T cells evident at this location in AR. Once induced, this inflammatory process within the nasal mucosa persists for several weeks after allergen exposure (29). In cases of PAR

where there is continuous low-dose allergen exposure, there is persistent nasal mucosal inflammation (30).

The concept that the mechanisms of disease generation provide a framework for rational therapy in this disorder is based on the complex inflammatory reaction rather than on the symptoms alone.

3. Allergen avoidance

The triggering event of AR is the contact of the responsible allergen with the nasal mucosa. This event, mainly through the degranulation of mast cells, leads to the clinical early-phase response and initiates the subsequent allergic inflammatory process. The severity of the disease and its natural course correlate well with the allergen concentration in the environment (31–33). Thus, the first therapeutic approach to the control of symptoms is prevention, by identification and avoidance of the causal allergen(s) (4, 34). The removal of the allergen has been proven to result in improvement in the severity of the allergic disease (35) and reduction of the need for drugs. The beneficial effect of environmental control may take weeks or months to be fully perceived. In most cases, complete avoidance of the allergen is not feasible due to practical and/or economic reasons. Nevertheless, allergen-avoidance measures should be considered before or in association with pharmacologic treatment, where appropriate.

As far as house-dust mites are concerned, there are some general and specific measures to be adopted for reducing the mite population and the allergen exposure. These measures ideally include:

1) removal of carpets and soft toys from the bedroom
2) use of allergen-impermeable (water-vapour permeable) covers for mattresses, duvets, and pillows
3) careful vacuum-cleaning of beds every week with a paper filter cleaner and damp-cleaning of furniture in the bedroom
4) washing bedclothes at 60°C.

Some acaricides (benzyl benzoate, tannic acid, etc.) appear to be effective in reducing the mite population if used regularly (36–38), but their clinical outcome remains unproven, and the use of allergen-impermeable covers for mattresses seems to be more effective (39–41).

A recent meta-analysis in asthma did not reveal clear evidence of the benefits of measures to avoid house-dust mites (42). However, optimal reduction of mite levels was frequently not achieved, thus not allowing a reduction of symptoms, and similar studies in rhinitis are not available.

The only effective measure for avoiding animal-dander allergens is to remove the pet (cat, dog) from the house and to vacuum-clean carefully all carpets, mattresses, and upholstered furniture. However, even with these measures, it may not be possible to eradicate cat allergens. Although frequent washing of cats reduces allergen recovery in the lavage (43), clinical studies have not shown clear benefit from this procedure when carried out once a week (44). If removal of the cat is not acceptable to the patient, the pet should at least be excluded from the bedroom or kept outdoors. Avoidance of pollen is often impossible due to its ubiquitous nature.

4. Oral antihistamines

General aspects

Histamine is a major mediator involved in the development of AR symptoms: the increase of histamine concentration in nasal secretions of atopic patients after nasal allergen challenge and during natural allergen exposure has been clearly demonstrated (45, 46). The role of histamine in the nasal allergic reaction is also confirmed by the reproduction of nasal symptoms after provocation with histamine. These symptoms – with the exception of obstruction – can be reduced by administering H_1-antagonists. Three histamine receptors are presently recognized, but the nasal effects of histamine are predominantly H_1-mediated. H_1-receptor antagonists reduce the clinical expression of nasal itching, sneezing, and rhinorrhoea, but they are less effective in controlling nasal obstruction (47, 48).

Efficacy

The use of the first-generation antihistamines (chlorpheniramine, diphenhydramine, promethazine, and tripolidine) is considerably limited by their sedative and anticholinergic effects; in addition, their short half-lives discourage the use of these antihistamines for AR treatment. The newer antihistamines (acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, loratadine, mizolastine, and terfenadine) are effective in reducing nasal symptoms such as itching, sneezing, and watery rhinorrhoea but have less effect on nasal blockage (49, 50) (for review, see refs. 4, 51–57) (Table 2). Antihistamines taken orally have the additional advantage of reducing nonnasal symptoms such as conjunctivitis and urticaria (58). Some experimental

Table 2. Characteristics of pharmacologic treatments

Characteristic	Oral antihist.	Nasal antihist.	Nasal steroids	Nasal decong.	Ipratropium bromide	Nasal cromone
Rhinorrhoea	++	++	+++	o	++	+
Sneezing	++	++	+++	o	o	+
Itching	++	++	+++	o	o	+
Blockage	+	+	+++	++++	o	+
Eye symptoms	++	o	++	o	o	o
Onset of action	1 h	15 min	12 h	5–15 min	15–30 min	Variable
Duration	12–24 h	6–12 h	12–48 h	3–6 h	4–12 h	2–6 h

+ Marginal effect; ++++ substantial effect (under natural exposure conditions).

studies showed additional effects of some of the newer antihistamines on mediator release (leukotrienes and histamine), on local inflammatory cell influx, and on the allergen-induced ICAM-1 expression on epithelial cells in both the early and the late phase after nasal allergen challenge (59, 60). However, the biologic effects of these drugs on mucosal inflammation and the clinical relevance of these non-H_1-receptor-mediated antiallergic properties remain to be established. Not all studies have shown that antihistamines have antiallergic properties (49, 61–63). The H_1-antagonists have a rapid onset of action (within 1–2 h) and a duration of activity of up to 12–24 h (except for acrivastine, which has a shorter activity). These H_1-antihistamines show individual differences in metabolism and pharmacokinetics.

Safety

Acrivastine, astemizole, ebastine, loratadine, and terfenadine are transformed into active metabolites in the liver by the cytochrome P450 system. Mizolastine is active per se and is largely metabolized through glucuronidation. Cetirizine and fexofenadine differ from other antihistamines in that they are not metabolized in the liver, but they are mainly excreted unchanged in the urine or in the faeces (64). The cytochrome P450 system is also responsible for the metabolism of other drugs that compete for the active site of the enzyme. The concomitant administration of azolic antifungal agents, such as ketoconazole, or macrolide antibiotics, such as erythromycin, may thus induce elevated concentrations of unmetabolized parent drugs. Grapefruit juice may have similar effects. These interactions have been particularly shown with terfenadine and astemizole. For drugs such as these, which interfere with the cardiac repolarization cycle, this increase in concentration may cause QT prolongation and increase risk of serious cardiac arrhythmia (including torsade de pointes) (65). These possible, but extremely rare, cardiotoxic effects are related to the dose-dependent capacity of the parent compound to block the K^+ channel of the ventricular myocyte, which plays a central role in ventricular repolarization. As a result, astemizole and terfenadine have been withdrawn from the market in several countries (66). At the present time, although reports on cardiac side-effects in a few patients using second-generation antihistamines have been gathered, there is no clinical evidence of a causal relationship with the exception of terfenadine and astemizole. Consequently, these drugs can be considered safe, if the drug-specific recommendations are followed, if concurrent administration of interactive drugs is avoided, and if patients with known liver impairment or at significant risk of cardiac rhythm disturbance are excluded. In patients at risk, antihistamines which are not metabolized and which do not have quinidine-like actions should be chosen (65).

The second-generation antihistamines induce significantly fewer undesirable CNS and anticholinergic effects than their first-generation predecessors. From the available data on the topic, the new H_1-antagonists have little or no sedative effect at the recommended dosage, which is in the range of placebo treatment in most of the studies (65–68). Increased appetite and weight gain can be a problem with astemizole (69).

Recommendations

In conclusion, because of their favourable risk-benefit ratio at standard clinical dose, satisfactory pharmacokinetics, and capacity to relieve nasal and nonnasal symptoms, the second-generation antihistamines can be considered the first-choice treatment for AR as far as disease severity and symptomatology are concerned. Antihistamines which can be administered once daily are preferred, and the recommended dosages should not be exceeded.

Antihistamines plus decongestants

H_1-receptor antagonists are effective on rhinorrhoea, sneezing, and itch, but in most studies they showed only limited effects on nasal obstruction. Thus, the association with oral decongestants (usually pseudoephedrine) has been introduced to compensate for this disadvantage. The available studies on combinations generally demonstrated a better reduction of global nasal symptoms as compared to the antihistamine alone (70, 71). However, these combinations do cause more insomnia and nervousness (side-effects due to pseudoephedrine). Moreover, children and elderly persons, who may be more susceptible to these effects, have not been sufficiently studied.

5. Topical antihistamines

General considerations

At present, two topical antihistamines are commercially available for the treatment of AR: azelastine and levocabastine. Both these drugs are effective and highly specific H_1-receptor antagonists. Azelastine and levocabastine nasal sprays promptly relieve itching and sneezing, and, when used twice daily regularly, they can also prevent the onset of symptoms (72, 73).

Efficacy

Azelastine and levocabastine have been developed both as eye-drops and as nasal spray for the topical treatment of allergic rhinoconjunctivitis (74–77). They demonstrate a similar efficacy profile to oral antihistamines with the advantage of a significantly faster onset of action on both nasal and ocular symptoms (78, 79).

Topical treatment is, however, specific to the site of administration.

Safety

In general, both azelastine and levocabastine topically administered at recommended doses do not show any significant sedative effect (76, 77, 80). One specific side-effect, a short-lasting perversion of taste, has been described for azelastine (81).

Recommendations

Topical antihistamines have a rapid onset of action (less than 15 min) at low drug dosage, but their action is limited to the treated organ. Topical antihistamines usually require bidaily administrations to maintain a satisfactory clinical effect. Their use may therefore be recommended for organ-limited mild disease and as an "on demand" treatment in addition to a continuous medication.

6. Topical corticosteroids

General aspects

Since the introduction of beclomethasone in 1973, topical treatments have been successfully used in AR (82). Subsequently, several new topical corticosteroids have been developed and marketed; they include budesonide, flunisolide, fluocortinbutyl, fluticasone propionate, mometasone furoate, and triamcinolone acetonide (the commercial availability of these products depends upon the country). Some of these compounds have a once-a-day regimen. All these molecules are now administered by mechanical pump sprays or as dry powder, since CFCs are to be banned. Corticosteroids have a strong anti-inflammatory capacity in reducing cytokine and chemokine release and are able to decrease the cellular infiltration of antigen-presenting cells, T cells, and eosinophils within the nasal mucosa (83–86), while mast cells are reduced to a lesser extent (83, 84).

Efficacy

Regular prophylactic use of topical corticosteroids is effective in reducing nasal blockage, rhinorrhoea, sneezing, and itching in adults and in children (87–89). A number of placebo-controlled clinical studies have proven the efficacy in SAR (90–92) and PAR (93–97). Extensive reviews of the clinical studies are available for beclomethasone dipropionate (98), budesonide (99), fluticasone propionate (100), mometasone furoate (86, 93), and triamcinolone (101), all agreeing on the clinical efficacy of these compounds. Other studies demonstrated that topical corticosteroids are more effective than systemic antihistamines (102, 103), topical antihistamines (104), and topical cromoglycate (105, 106). A recent meta-analysis has confirmed the superiority of topical corticosteroids to antihistamines in the treatment of AR for all nasal symptoms (107).

Safety

The current intranasal preparations are well tolerated and can be used on a long-term basis without atrophy of the mucosa (108). Topical steroids may occasionally cause local side-effects, such as crusting, dryness, and minor epistaxis, but these side-effects are mild (92, 93, 97, 100). Septal perforations due to prolonged use of topical corticosteroids have been described only anecdotally (109).

Patients receiving only nasal corticosteroids appear to be at low risk of developing hypothalamic-pituitary-adrenal axis (HPAA) suppression because of the low drug availability and the low doses used (110). Studies have shown that intranasal corticosteroids have no effect on the HPAA, except for dexamethasone spray and betamethasone drops, which can rarely provoke systemic effects (86, 93, 111–113). The newer nasal steroids fluticasone propionate and budesonide usually show no effect on the HPAA (108, 114, 115). However, one recent abstract describes an effect on children's growth by beclomethasone (116). In view of recent concerns (FDA, MCA), more data are required on the safety of intranasal steroids in young children.

Patients with rhinitis often have comorbidity with disorders such as asthma, and these patients may use both inhaled and intranasal corticosteroids. Caution is necessary to avoid adverse events in these patients. For further detailed information, we refer to a recent EAACI position paper on the clinical safety of inhaled and nasal corticosteroids (*Allergy* 2000;55:16–33).

Recommendations

The effect of topical corticosteroids on nasal blockage and their anti-inflammatory properties favour them above other treatments, especially in PAR, in circumstances where obstruction is the main symptom, and in long-lasting disease. They have a relatively slow onset of action (12 h), and maximum efficacy develops over days and weeks. When the nose is extremely congested, nasal corticosteroids may not easily reach the mucosa, and it may be advisable to give a topical decongestant (e.g., xylomethazoline) or systemic steroids for not more than a week. Topical corticosteroids should be given regularly and may be commenced before the beginning of the pollen season in severe cases for maximal effect.

In conclusion, topical corticosteroids can be regarded as a highly effective first-line treatment for patients suffering from AR with moderate to severe and/or persistent symptoms.

7. Systemic corticosteroids

General aspects

Systemic corticosteroids are not the first line of treatment for AR; they are a last resort. Although these drugs are frequently used in clinical practice, there are relatively few scientific data available to support this use. There is a lack of comparative studies on the preferred dose, the route of administration, and the dose-response relationship.

Steroids can be given orally (e.g., prednisolone, starting dose 20–40 mg/day) or as a depot injection (e.g., methylprednisolone 40–80 mg/injection) (117). Systemic corticosteroids exert their action on a broad spectrum of inflammatory phenomena and are effective on most symptoms of rhinitis, especially obstruction and loss of smell.

Efficacy and safety

No information is available on the efficacy and safety of repeated administration of depot corticosteroids. The only controlled comparison between oral and injected steroids in rhinitis showed a therapeutic index in favour of the depot injection (118). Nevertheless, there are arguments in favour of oral administration (119). It is cheap, and the dosage can be adjusted to the changing need for treatment. Moreover, it must be remembered that an injection of 80 mg methylprednisolone corresponds to 100 mg prednisolone, and that continuous release during the day will suppress the HPAA more than a single oral dose given in the morning. Since the risk of adverse effects from systemic corticosteroids largely depends upon the duration of treatment, only short-term courses (3 weeks) should be prescribed in rhinitis; the side-effects from a 3-week treatment are mostly few and mild. In rare cases, depot injections can cause a depression over the injection site, due to tissue atrophy. The local administration of depot injections into swollen nasal turbinates and polyps should be avoided, since serious adverse events (blindness) have been reported.

Contraindications

Contraindications to systemic steroids are glaucoma, herpes keratitis, diabetes mellitus, psychologic instability, advanced osteoporosis, severe hypertension, tuberculosis, or other chronic infections.

Recommendations

When other treatments are inadequate in seasonal AR, the patient can be supplied with prednisolone tablets in the morning during troublesome periods. Oral steroids have the advantage over depot injections that treatment can follow the pollen count. In contrast to topical treatment, systemic steroids reach all parts of the nose and the paranasal sinuses; therefore, short courses in patients with severe perennial rhinitis or nasal polyposis can be helpful.

In conclusion, systemic steroids are effective in controlling rhinitis symptoms, but they should not be used as first-choice treatment. In the case of severe symptoms refractory to first-choice treatments, short courses (<3 weeks) of oral steroid therapy can be prescribed; ideally, no more frequently than every third month. Systemic steroids should be avoided in children, pregnant women, and patients with known contraindications.

8. Cromones

General aspects

The cromones used in the treatment of allergic diseases are disodium cromoglycate (cromolyn, DSCG) and sodium nedocromil. The action of these drugs is linked to the cell wall of the mast cell and/or to the intracellular events that follow the allergen binding to IgE. The mechanism of action is still unknown. Blockage of the Ca^{2+} channels on the mast-cell membrane, phosphodiesterase inhibition, or blockage of oxidative phosphorylation has been suggested. *In vitro*, sodium nedocromil has been shown to inhibit the activation of neutrophils, eosinophils, monocytes, macrophages, and mast cells (120, 121). A "local anaesthetic" effect has also been proposed, as has an inhibitory effect on sensory neural stimulation (122).

Efficacy and safety

Although two studies showed equivalent efficacy of cromones and terfenadine, the efficacy of cromones in SAR has been questioned, especially when compared to topical corticosteroids and antihistamines (105, 123, 124). Comparisons between topical corticosteroids and DSCG or topical antihistamines and DSCG in patients with seasonal AR demonstrated the greater efficacy of both drugs over DSCG, for both symptom control and patient compliance (due to the multiple daily administration necessary for DSCG) (105, 122). In childhood AR also, topical corticosteroids were shown to be more effective than DSCG (106). The observation of unsatisfactory compliance with a drug requiring four to six daily administrations was also confirmed. Sodium nedocromil showed a measurable clinical efficacy in AR (125), especially in the seasonal form when compared to placebo (126, 127), and the combined therapy nedocromil plus astemizole appeared more effective than the antihistamine alone (128). Both DSCG and sodium nedocromil are safe and almost totally devoid of side-effects.

Recommendations

The efficacy reported for DSCG is inferior to drugs such as antihistamines and steroids. Sodium nedocromil seems to have an only slightly greater efficacy and a more rapid onset of action. Therefore, cromones cannot be considered a major therapeutic option in the treatment of AR, although they have a role in the prophylactic treatment of conjunctivitis (129) or in mild and early rhinitis.

9. Decongestants

General aspects

The decongestant (or vasoconstrictor) drugs affect the sympathetic tone regulation of blood vessels by acting on adrenergic receptors and provoking vasoconstriction. Decongestants available for clinical use include α_1-adrenergic agonists (e.g., phenylephrine), α_2-adrenergic agonists (e.g., oxymetazoline, xylometazoline, naphazoline), noradrenaline releasers (e.g., ephedrine, pseudoephedrine, phenylpropanolamine, amphetamines), and drugs preventing the re-uptake of noradrenaline (e.g., cocaine, tricyclic antidepressants, phenylpropanolamine) (130).

Efficacy

Topical decongestants are very effective in the treatment of nasal obstruction. It was demonstrated that xylometazoline reduced the nasal airway resistance (NAR) for up to 8 h with a maximal fall in NAR of 33%, while phenylephrine decreased the NAR over 0.5–2 h with a maximal fall in NAR of 17% (131). The long-lasting effect of oxymetazoline and xylometazoline may be explained by their slow mucosal clearance due to the decreased mucosal blood flow (132).

Oral vasoconstrictors such as ephedrine, phenylephrine, phenylpropanolamine, and especially pseudoephedrine are the most commonly used systemic nasal decongestants. Generally, they have a weaker effect on obstruction than the topical decongestants, but they do not cause rebound vasodilatation.

Safety

Most of the studies with topical decongestants show that short-term courses of treatment do not lead to functional or morphologic alterations. Prolonged use (>10 days) of topical vasoconstrictors may lead to tachyphylaxis, rebound swelling of the nasal mucosa, and "drug-induced rhinitis" (rhinitis medicamentosa).

Recommendations

In general, because of the risk of rhinitis medicamentosa, the use of topical decongestants should be limited to a duration of less than 10 days. Short courses of topical decongestants can be used to reduce severe nasal blockage promptly while coadministering other drugs. Decongestants should be used with care in children under 1 year of age, because of the narrow range between therapeutic and toxic dose (4). Furthermore, it is advisable not to prescribe pseudoephedrine to young children (<1 year) and adults over 60 years; to pregnant women; to patients suffering from hypertension, cardiopathy, hyperthyroidism, prostatic hypertrophy, glaucoma, and psychiatric disorders; and to patients taking beta-blockers or MAO inhibitors.

10. Anticholinergic agents

General aspects

Parasympathetic fibres originate in the superior salivatory nucleus of the brainstem and relay in the sphenopalatine ganglion before distributing to the nasal glands and blood vessels (133). Parasympathetic stimulation causes a watery secretion, mediated by the classical autonomic transmitter acetylcholine, and vasodilatation of blood vessels serving the glands. The muscarinic receptors of the seromucinous glands can be blocked by the anticholinergic drug ipratropium bromide (134), which is commercially available in several countries as a nasal spray (pressurized aerosol, to be replaced by an aqueous pump spray). The total daily dose recommended by authors ranges between 120 and 320 μg given in three to six administrations (134, 135).

Efficacy

Ipratropium bromide is effective in controlling watery nasal discharge, but it does not affect sneezing or nasal obstruction. Double-blind, placebo-controlled trials have shown that ipratropium bromide can reduce rhinorrhoea in perennial nonallergic (vasomotor) rhinitis (135–140), common cold (141), and rhinitis in elderly people (142), but little information is available on its efficacy in AR. A single dose of 42 μg per nostril reduces the secretion due to methacholine stimulation for 3 h; 168 μg doubles the effect (48% reduction) and its duration in perennial nonallergic rhinitics (143, 144). The onset of action is fast (15–30 min). Recent studies in PAR (144–147) indicate a possible benefit of ipratropium bromide, as it reduced the severity and duration of secretion by 30–40%.

Safety

Topical side-effects due to the anticholinergic action are common and obviously dose-dependent in their severity. Nasal dryness, irritations, and burning are the most prominent effects, followed by stuffy nose, dry mouth, and headache (135, 140, 148). Olfaction, ciliary beat frequency, epithelial light microscopy, and clinical

appearance of the nasal mucosa are not affected even by long-term use. Systemic side-effects are rare (134, 135, 149), but they can occur with doses higher than 400 μg/day (149).

Recommendations

The few studies performed in PAR demonstrated that ipratropium bromide improves only nasal hypersecretion, whereas no data are available for seasonal rhinitis. Therefore, since patients usually also suffer from nasal congestion, itching, and sneezing, other drugs are preferable to ipratropium in the vast majority of cases of AR.

11. Subcutaneous immunotherapy (therapeutic vaccines)

General aspects

Subcutaneous immunotherapy (SIT) has been empirically used in the treatment of respiratory allergy since 1911; since the 1970s, its efficacy has been documented in a large number of controlled studies, and its mechanisms of action have been recently partly elucidated. For further detailed information, we refer to the WHO position paper on allergen immunotherapy (150). The introduction of purified and standardized extracts and the rigorous definition of its indications, contraindications, and rules for prescription have confirmed SIT as an effective and reliable prophylactic treatment for AR (151). A SIT course usually involves a build-up phase (increasing allergen doses) and a maintenance phase (maximum dosage of the allergen) in which the extract is administered with a 1–2 month interval.

Efficacy

The efficacy of SIT for rhinitis in carefully selected patients appears to be well documented. Since 1980, there have been 43 placebo-controlled, double-blind studies (152). They comprise 13 studies investigating ragweed allergy (nine demonstrating efficacy), 15 investigating grass-pollen allergy (14 favourable), nine investigating other allergens (mountain cedar, *Parietaria*, *Cocos*) (six demonstrating efficacy), and five investigating mite allergy (three favourable). The efficacy for cat extract has been documented in patients suffering from both rhinitis and asthma; for mould allergy, the validation of efficacy is limited to one study investigating *Alternaria* (153). In a study by Varney et al. (154) in patients allergic to grass pollen uncontrolled by standard antiallergic drugs, SIT led to a reduction in symptoms and use of drugs in the actively treated group to about a quarter of the levels in the placebo group. When evaluating these studies for efficacy, only clinically relevant improvement in disease severity should be accepted (151). This is supported by a recent study which showed a reduction in the development of multiple allergic sensitivities in children who received SIT at an early stage (155). Two recent studies also show that an adequate course of treatment (3–4 years of SIT) may induce prolonged remission (156). Taken together, these studies show that SIT should be considered a supplement to drug therapy and possibly be used earlier in the course of allergic disease, in order to achieve maximum benefit.

Safety

SIT entails the risk of systemic anaphylactic reactions (157), but this risk is low. The rate of systemic reactions in rhinitics treated with high-potency extracts is approximately 5% of the patients (158), primarily in the build-up phase (151). However, the risk is real: therefore, the indication and the practical treatment have to be performed by clinicians trained in resuscitation (151). Special care is necessary in patients with concomitant asthma (159).

Recommendations

SIT is indicated for patients with evidence of a clinically relevant IgE-mediated disease and a limited spectrum of allergies (one or at most two clinically relevant allergens) and in whom pharmacotherapy and avoidance measures are insufficient (150). Further considerations are patients' attitude to available treatment modalities, costs of treatment, and the quality of allergen vaccines available for treatment (160). The indications for SIT in asthma and rhinitis have been separated in some guidelines (4, 34, 161), and this artificial separation has led to unresolved questions (162–164), possibly because the allergic reaction has not been considered to have multiple organ involvement. It is therefore important to consider SIT based on allergen sensitization rather than a particular disease manifestation. The risk/benefit ratio should be considered in all cases (150). However, in carefully selected patients and provided that therapy is administered by specialists, SIT may be highly effective. Although at present reserved for "difficult" care, recent data suggest that SIT should be introduced earlier in the course of allergic disease.

12. Local (noninjective) routes for immunotherapy

General aspects

The possibility of desensitizing the specific target organs of respiratory allergy has been envisaged since the beginning of the century (165), but only in recent years have some immunologic and pharmacokinetic studies provided experimental support for such an approach (166–169). The claims of possible severe side-effects (170) in SIT further encouraged the development of

local (or noninjective) routes, and several double-blind, placebo-controlled studies were published (171).

Efficacy

An extensive critical review of the clinical studies is available in the EAACI/ESPACI position paper (172). Thirteen out of 14 controlled studies presently available agree on the clinical effectiveness of local nasal immunotherapy (LNIT) in reducing symptoms of pollen- and mite-induced rhinitis and the specific nasal reactivity. Concerning pollens, the protective effect on natural allergen exposure appeared to depend on the preseasonal administration of the treatment (173). Sublingual immunotherapy (SLIT) was proven to be effective in seven (out of seven) controlled studies: it was capable of improving symptoms of rhinitis due to mite, *Parietaria*, and grass pollen and capable of reducing allergic inflammation (174). In the only available double-dummy study, SLIT appeared to be as effective as SIT (175). The majority of the clinical studies have been conducted in adult patients. Oral immunotherapy and bronchial immunotherapy are presently not sufficiently supported by experimental evidence (172).

Safety

In the earliest LNIT studies, aqueous extracts were effective but they often caused LNIT-induced rhinitis; with the new powdered extracts, this problem seems to have been satisfactorily overcome. In SLIT, oral itching and gastroenteric side-effects have been described rarely; in most studies, their occurrence did not differ from placebo. No life-threatening reactions or deaths have ever been described with local routes.

Recommendations

Properly controlled, well-designed studies employing sublingual/swallow and intranasal immunotherapy provide evidence that these routes may be a viable alternative to SIT, as recently stated by the WHO position paper (150). The clinical effectiveness of LNIT and SLIT has been clearly proven for seasonal AR, while fewer studies are available for PAR. LNIT and SLIT are administered through a build-up phase, followed by a maintenance phase of the maximum dosage, administered twice weekly. The LNIT administration may be preceded by cromolyn premedication, and the patient must vocalize during insufflation. The indications do not differ from those of SIT; a detailed etiologic diagnosis and a careful evaluation of the cost/benefit ratio are always required. Further studies are needed fully to characterize the most appropriate patients, the optimal therapeutic target dose, and the use in pediatric patients.

13. Pediatric aspects

In principle, treatment of AR in children does not differ from that in adults. However, dosages have to be adapted and some special considerations are required. On one hand, special caution is necessary because of the young age of the patients, but, on the other hand, an early appropriate treatment may have not only therapeutic, but also prophylactic effects, as was shown recently (176–178). Few drug treatments are available under the age of 2 years. Nasal saline drops or spray can help to clear the nose before eating or sleeping. Treatment of AR in children under the age of 4 years again depends on allergen avoidance, but sodium cromoglycate and oral antihistamines are also available for this age group. Cromones are weakly effective, and compliance may be poor due to the need of regular use several times a day (179, 180). Antihistamines, topical and oral, are effective and well tolerated, but especially first-generation antihistamines may reduce academic ability in schoolchildren (11, 179). Fluticasone propionate is available for children of 4 years and over, and other topical corticosteroids may be used in children over the age of 5 years. Topical corticosteroids are highly effective, but care must be taken to avoid systemic side-effects, especially on growth (116). The modern corticosteroids are much less absorbed (bioavailability $<30\%$), and the minimal dose needed to control symptoms should be used (181, 182). Corticosteroids with high bioavailability (183) and systemic corticosteroids (184) are not suitable in children.

Treatment options:

Local:
- Sodium nedocromil
- Disodium cromoglycate
- Azelastine or levocabastine (>5 years)
- Beclomethasone dipropionate (>5 years)
- Flunisolide (>5 years)
- Fluticasone propionate (>3 years)
- Triamcinolone acetonide (>6 years)

Oral:
- Cetirizine (5 mg>2 years, 10 mg>6 years)
- Ketotifen (1 mg b.i.d.>2 years)
- Loratadine (5 mg<30 kg body weight, 10 mg>30 kg)

14. Practical guidelines for the treatment of SAR and PAR, and nonallergic noninfectious rhinitis

As in the 1994 guidelines, it was decided to follow a stepwise approach in the treatment of allergic and nonallergic rhinitis, because this seems to be the most practical approach for the practitioner, the general practitioner as well as the specialist.

Unlike the 1994 guidelines, not only are the mild and moderate cases considered, but also the severe ones. Consequently, the present guidelines are also aimed at the specialist. It is assumed that a correct diagnosis has been achieved before treatment.

Definition of terms

It is necessary to define what is meant by "mild", "moderate", and "severe", and also the terms "occasional", "long duration", and "frequent symptoms".

Mild means that the patient has only a few symptoms not interfering with daily activities and/or sleep. The patient realizes that the symptoms are present and wants treatment, but can do without it if necessary.

Moderate means that the symptoms are important enough to disturb the patient during daily activities and/or sleep. The patient really wants treatment because his/her quality of life is clearly diminished.

Severe means that the symptoms are so pronounced that the patient cannot function properly during the day and/or cannot sleep if no treatment is given.

Occasional means that the symptoms are bothersome for less than 14 days in the case of SAR and less than 1 month in perennial rhinitis.

Long duration in the case of SAR means that the patient suffers for a period of more than 2 months. This can be due to allergy to pollen with a long pollination period (e.g., grasses) or to allergy to several kinds of pollen with different periods of pollination (e.g., allergy to tree and grass pollen).

Frequent symptoms in the case of perennial rhinitis means that the patient has troublesome symptoms for at least 2 days a week for a period of at least 3 months a year.

Availability of the treatment

The guidelines assume that the suggested treatments are available and affordable to the patient. A dissemination programme of the present guidelines, sponsored by the IAACI, which is called GLORIA, will also take into account situations where the treatment suggested as first choice is unavailable to and/or financially unaffordable for the patient. These data will be available at the end of 2001.

General remarks on how to interpret and how to follow the practical guidelines for the treatment of rhinitis

The suggestions have been made by a panel of experts (the authors) and are based on the literature data available by May 1999. A full consensus was reached on all of the material presented in this position paper. The panel recognizes that the suggestions it puts forward are valid for the majority of patients within a particular classification but that individual responses of patients to a particular treatment may differ from those suggested for a given therapy.

The guidelines do not take into account the costs of the treatment. They assume that all treatments are readily available and financially affordable to the patient (on health insurance). Alternative treatment modalities such as homoeopathy, phytotherapeutics, acupuncture, and bioresonance are not sufficiently validated, entail the risk of serious side-effects, or must be considered frivolous, and therefore are not recommended.

Seasonal allergic rhinitis

Some patients have a proven sensitization to pollen but do not present troublesome symptoms under any circumstances. No treatment or avoidance measures should be taken in such cases (Fig. 1).

If the symptoms are mild or occasional but the patient wants treatment, antihistamines are recommended. If the patient has both nasal and eye symptoms, an oral antihistamine (nonsedative, second-generation) is recommended. If only nasal symptoms are bothersome, we have a choice between an oral antihistamine and a topical nasal antihistamine. If only eye symptoms are bothersome or not controlled by an oral antihistamine, a topical ocular antihistamine is recommended (with or without an oral antihistamine or a topical nasal antihistamine in case of bothersome nasal symptoms). In mild cases, an alternative to antihistamines is the use of topical cromones for the nose or eyes, preferably starting this topical treatment before the season starts and throughout the whole season.

If the patient presents with moderate symptoms or symptoms of long duration or if the symptoms are mild but not controlled by antihistamines (or cromones), a topical nasal steroid is recommended throughout the season on a regular daily basis. This advice is valid for both adults and children. If the concomitant eye symptoms are bothersome and not sufficiently controlled by the nasal steroid, a topical ocular antihistamine or cromone is recommended in addition to the nasal steroid.

If the patient presents with severe symptoms or if the treatment with nasal steroids in the case of moderate disease does not have an adequate effect, a combination of nasal steroids and antihistamines (oral and/or topical) is recommended, or a different compound or delivery system of the same class, or an increase of the dosage without exceeding – in children – the range of the recommended dose.

If these measures do not give sufficient relief of the symptoms, the panel recommends further symptomatic treatment, such as (oral or topical) decongestants in the case of nasal obstruction, ipratropium bromide in the

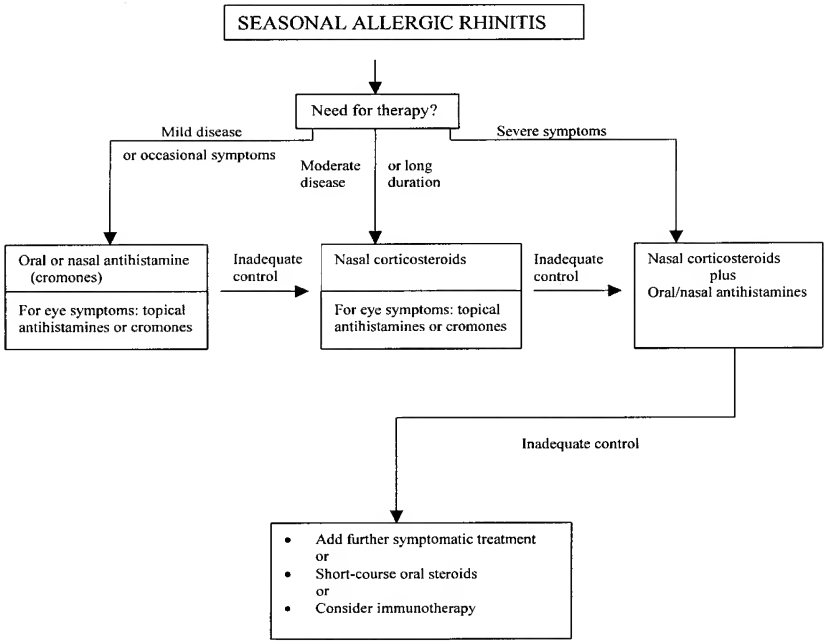

Figure 1. Stepwise therapeutic approach in seasonal allergic rhinitis.

case of watery rhinorrhoea, analgesics in the case of headache, or a short course of oral steroids.

When patients present severe symptoms that are difficult to control, immunotherapy should be considered, starting 2 months after the pollen season.

Perennial allergic rhinitis

In adults

Sometimes symptoms are not bothersome enough to make treatment necessary (Fig. 2). Avoidance measures can be taken in this case, without too much effort to eradicate the allergens, mostly house-dust mites, especially since it is not yet proven that an effective reduction of allergen exposure is possible and beneficial in terms of symptom reduction.

If the patient finds treatment necessary, then the environmental control should be more thorough in trying to reduce the need for pharmacologic treatment (or immunotherapy).

In mild cases or when the symptoms are intermittent, the use of antihistamines (oral or nasal) is recommended when symptoms are present.

If the symptom control with antihistamines is inadequate or if the patient presents to the physician from the start with moderate or frequent symptoms, a topical steroid is recommended for long-term use up to several months. After 3 months of successful treatment, the therapy may be interrupted to be started again if the symptoms reappear; in this case, it depends on the severity of the symptoms at recurrence whether a nasal steroid (moderate of frequent symptoms) or an antihistamine (mild or occasional symptoms) is recommended.

If the symptoms are not controlled by topical steroids alone or if the patient presents with severe symptoms from the start, a combination of topical steroids and oral antihistamines is recommended. When the symptoms are sufficiently controlled by this combination, one should try to stop the topical steroid or the antihistamine, depending on the severity and pattern of the remaining symptoms.

If the combination of nasal steroids and antihistamines still cannot provide sufficient relief from the symptoms, a new and thorough clinical investigation should be done in order to exclude underlying diseases that are of nonallergic origin, such as anatomical abnormalities, chronic sinusitis, nasal polyps, etc. These underlying diseases should be treated if they are judged responsible for (an important part of) the symptoms resistant to the given treatment.

If the patient still suffers after being treated for possible underlying disorders and after having been given topical steroids and antihistamines, the remaining symptoms will determine which further treatment should be given (Fig. 3). In cases of resistant nasal obstruction, we can give a short-term course of topical decongestants (not longer than 10 days in order to avoid rhinitis medicamentosa), or an oral decongestant (time unrestricted), or a short course of oral steroids.

If all medical treatment fails to relieve the nasal obstruction because of hyperplasia or pronounced

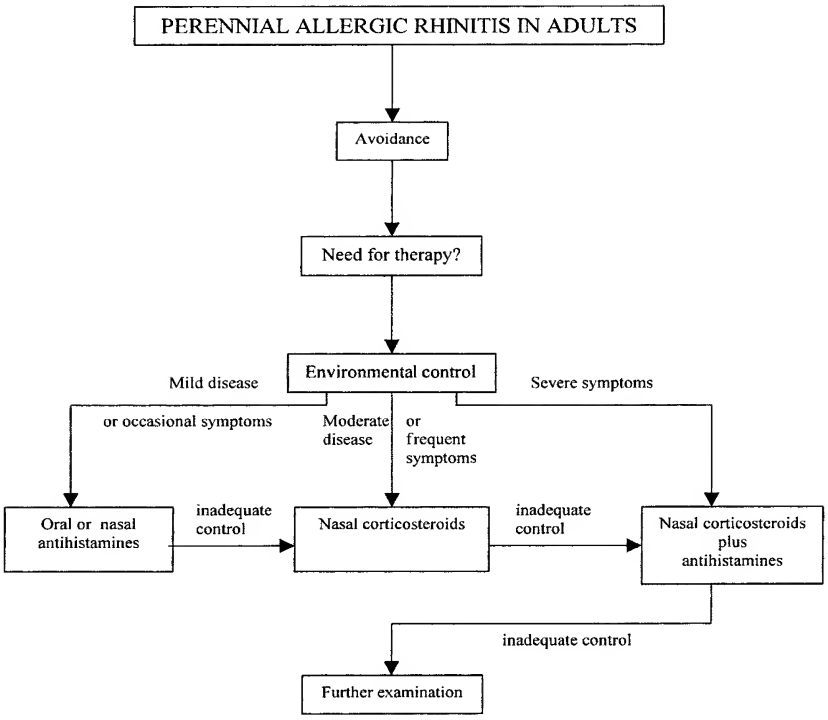

Figure 2. Stepwise therapeutic approach in perennial allergic rhinitis in adults.

hypertrophy of the inferior turbinates, a surgical reduction can be performed. It should always be as minimally invasive as possible in order to prevent secondary atrophic rhinitis due to a too aggressive reduction.

If a patient presents especially watery rhinorrhoea that is refractory to treatment, topical ipratropium bromide is advised. The dose varies from individual to individual. As long as the rhinorrhoea persists, we recommend increasing the dose until a certain dryness

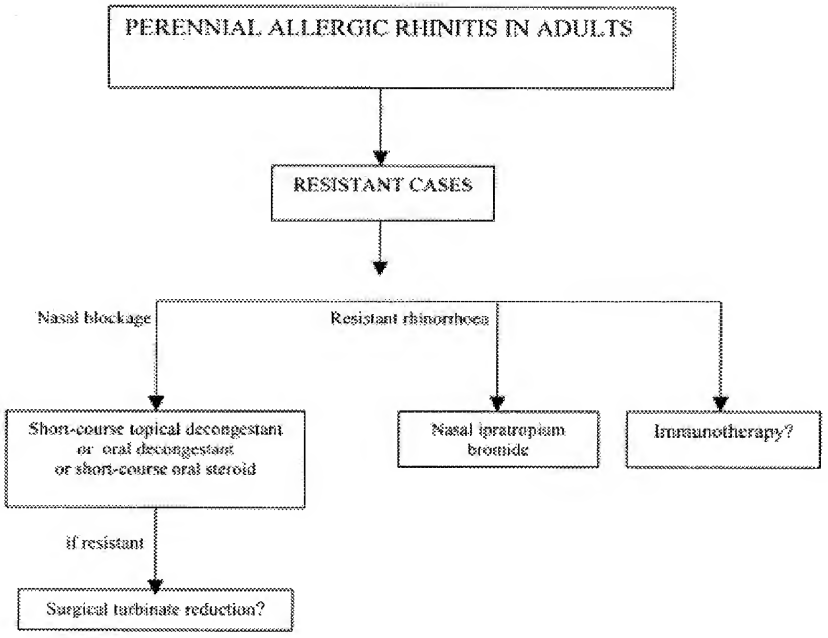

Figure 3. Stepwise therapeutic approach in resistant cases of perennial allergic rhinitis in adults.

in the nose is felt or until the maximum recommended dose is reached.

Immunotherapy is a treatment directed against all symptoms and the underlying inflammation. The results are not as good as in pollen allergy, but with house-dust mite and with certain animal dander, satisfactory results can be reached.

In children

The principles of the treatment of children are the same as in adults, but special care has to be taken to avoid side-effects which are typical of this age group (Fig. 4). Oral steroids should always be avoided in the treatment of PAR in young children. Avoidance of the responsible allergen is even more important in young children than in adults because of the risk of developing new sensitizations or additional tissue involvement.

When the symptoms are bothersome enough, strict environmental control is necessary to reduce symptoms and the need for further pharmacologic therapy or immunotherapy.

The first choice of treatment for any degree of symptoms is antihistamine treatment (oral or nasal). Nasal cromones are an alternative to antihistamines. If the treatment is started with cromones and is unsuccessful, we should proceed to antihistamine treatment. If antihistamines are not capable of sufficiently controlling the symptoms, we proceed to use topical nasal steroids at the recommended dose for the age of the child. Care should be taken with regard to the dosage if the child is already taking topical steroids to the lungs.

If the treatment with topical steroids is insufficient, the combination of topical steroids and antihistamines should be tried. If the symptoms are not controlled adequately by these treatments, immunotherapy should be considered.

Topical or oral decongestants are not recommended in young children because of the possible side-effects.

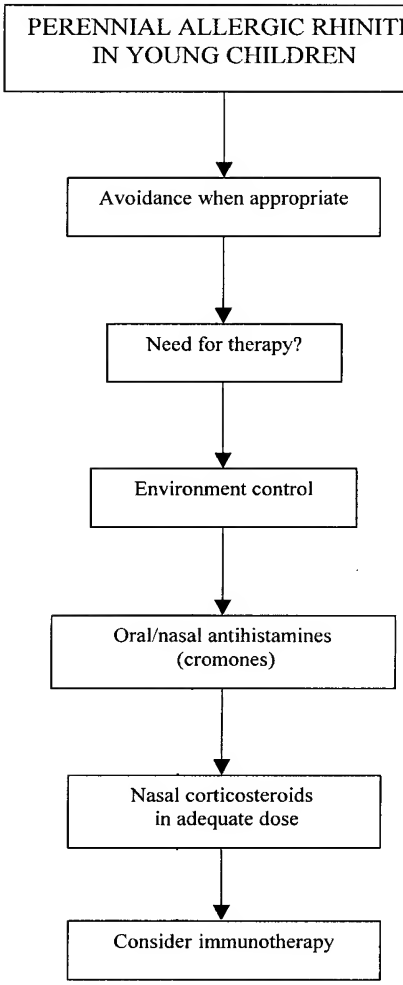

Figure 4. Stepwise therapeutic approach in perennial allergic rhinitis in young children.

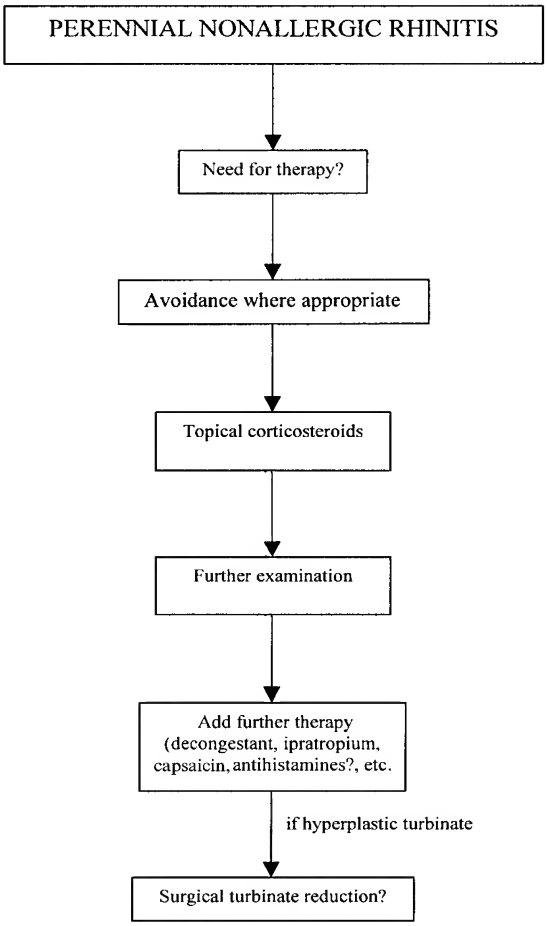

Figure 5. Stepwise therapeutic approach in perennial nonallergic rhinitis.

Perennial nonallergic rhinitis

The symptoms of perennial nonallergic rhinitis may vary from mild to severe, and include nasal obstruction, watery rhinorrhoea, and sneezing. The pathophysiologic mechanisms are diverse. The treatment results are usually not as good as in AR.

Some patients do not need any treatment because the symptoms are not bothersome. In some cases, patients can avoid the precipitating factors (Fig. 5).

If a treatment is indicated because of the severity of the symptoms, topical steroids should be given as the first attempt. If this is not adequate, further investigation should be done to exclude other nasal diseases (chronic sinusitis, polyposis, anatomical anomalies, tumour, etc.), systemic disorders (aspirin intolerance, side-effects of medication, hormonal disturbances, etc.), or noxious exogenous factors.

If this does not lead to improvement, further therapy can be added to the topical steroids: oral or short-term topical decongestants in the case of resistant nasal obstruction, topical ipratropium bromide in the case of watery rhinorrhoea, or, in the most severe cases, a short course of oral steroids. There is experimental evidence that treatment with capsaicin would help some of these patients (185).

If the nasal obstruction is resistant to medical treatment and if the inferior turbinate is hyperplastic, a reduction of the size of the turbinate can be helpful (cryosurgery, surgery).

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